REMARKS

Entry of the foregoing, reconsideration of the restriction requirement, and examination and favorable consideration of the subject application in light of the following remarks are respectfully requested.

By the present amendment, Claim 6 is amended to better recite the claimed subject matter. Support for the amendment to Claim 6 may be found in Claim 6 as originally filed. No new matter is believed to have been added by the foregoing amendment.

In response to the restriction requirement of the present Official Action, Applicants provide the following election **with traverse**.

I. First Election With Traverse Dated March 22, 2002

In Item 1 of the Detailed Action, the Examiner has acknowledged the Applicants previous election **with traverse** of Group I (claims 1, 2, 6 and 7) and the species "a protein." With respect to the search required for each group of the first restriction requirement, the Examiner states that, although related, they are not co-extensive. The Examiner asserts, therefore, that "a burden does exist, and restriction is appropriate."

However, this decision does not reflect full application of the standard set forth in the U.S. Patent and Trademark Office Manual of Patent Examination Procedure. **The standard is not that any burden warrants a restriction. There must be a serious burden on the Examiner for restriction to be required.** M.P.E.P. § 803 (8th ed. 2001). The Examiner has still not provided any showing that demonstrates that a serious burden will be imposed if restriction is not required. Therefore, the former restriction requirement is still improper. Since the Examiner has not stated that the first restriction requirement is final, Applicants respectfully request reconsideration and withdrawal of the first restriction requirement.

II. Status of the Claims

Applicants also note for the record that Item 2 of the Detailed Action and the Office Action Summary indicate that claims 3-6 and 8-47 have been withdrawn from further

consideration. This is inconsistent with the former restriction requirement and Applicants' election. The non-elected claims are 3-5 and 8-47.

III. Second Election with Traverse

In Item 3 of the Official Action, the Examiner has set forth a second restriction requirement in the subject application. The Examiner states that claims 1, 2, 6, and 7 are generic to a plurality of disclosed patentably distinct Restriction Subgroups of the claimed invention. The Examiner has required an election between Subgroups containing either SEQ ID NO:1 or one Zmax1 nucleic acid comprising a polymorphism of Table 4. A Markush group reciting these sequences is an element in claim 6, step (A). The Examiner further asserts that "these subgroups are independent and distinct because each molecule comprising each polymorphic site is structurally and functionally distinct because the chemical structure of the polymorphism differs from one another." Official Action at page 2. This second restriction requirement is respectfully traversed for at least the following reasons.

The M.P.E.P. requires that two criteria must be satisfied for a proper requirement for restriction: "(A.) The invention must be independent or distinct **as claimed**; and, (B.) There must be a serious burden on the Examiner if restriction [were not] required." M.P.E.P. § 803 (emphasis added). The present restriction requirement has not met the burden of showing either of these criteria. Furthermore, the present restriction requirement is inconsistent with the provisions of M.P.E.P. § 803.02 regarding the treatment of Markush groups. Therefore, the present restriction requirement is improper under the published policy of the U.S. Patent and Trademark Office.

A. The second restriction requirement is improper, because the particular reasons relied upon by the Examiner for holding that the invention as claimed are either independent or distinct have not been stated.

The M.P.E.P. requires that "[t]he particular reasons relied on by the Examiner for the conclusions of distinctness of **the invention(s) as claimed** should be concisely stated."

M.P.E.P. § 816 (emphasis added). The M.P.E.P. further states, "**[e]ach** . . . relationship of claimed invention should be . . . treated and the reasons for the conclusions of distinctness of **invention as claimed** set forth." *Id.* (emphasis added).

The present restriction requirement appears to be based solely on the unsupported conclusion that "each molecule comprising each polymorphic site is structurally and functionally distinct, because the chemical structure of the polymorphism differs from one another." Official Action at page 2. However, "[a] mere statement of conclusion is inadequate." M.P.E.P. § 816. In contrast to the Examiner's conclusory statement, the sequences that are the subject of the present restriction requirement, which comprise only one element of the claimed method, are related by both structure and function. For example, the Zmax1 nucleic acids comprising a polymorphism of Table 4 are related by structure in that each represents an allelic variant of the Zmax1 sequence. *See,* Specification at page 19, lines 6-7 and page 73, lines 11-12. The sequences are related by function in that these allelic variants of the Zmax1 sequence are found among relatives of the HBM affected persons. *See*, Specification at page 71, lines 21-24. However, only the G to T base change seen at position 582 of SEQ ID NO:2 (complementary to the C to A change at position 21119 in contig 308G) appears to be a primary cause of the HBM phenotype. Therefore, the non-HBM polymorphisms of Table 4 are functionally related in being allelic variants of Zmax1 which can be used, as in the presently claimed method, for identifying candidate molecules which interact differently with the HBM sequence than non-HBM allelic variants. For purposes of the claimed method, the functional interchangeability of the polymorphic variants recited in step A of Claim 6 is apparent from the claim itself.

It is true that any one sequence does not render another of the sequences obvious, and the sequences would be distinct if claimed as an isolated compound or if recited in a method in which the sequences were not interchangeable. However, the Markush group of sequences of claim 6, step (A) are not indicated as functionally distinct in the presently claimed method. Each allelic variant of the group can be used in the methods of the invention singly or together. "[T]wo different subcombinations usable with each other may

each be a species of some common invention." M.P.E.P. § 806.04(b) (citing *Ex parte Healy*, 1898 C.D. 157, 84 O.G. 1281 (Comm'r Pat. 1898)). Therefore, the polymorphic sequences are related for the purposes of the claimed method. *See, Id.* Because the sequences are related, it stands to reason that embodiments of the method incorporating the alternative sequences are related.

Where the species of an invention are related, the appropriate course of action is dictated by M.P.E.P. §§ 808.01(a), and 809.02(a-e). In the present case, only a generic claim 6 is presented. "Where only generic claims are presented, no restriction can be required except in those applications where the generic claims recite such a multiplicity of species that an unduly extensive and burdensome search is necessary." M.P.E.P. § 809.02(d). Otherwise, the Examiner must show by appropriate explanation, (A) separate classification, (B) separate status in the art, or (C) a different field of search. M.P.E.P. § 808.02. "Where, however, the classification is the same and the field of search is the same and there is no clear indication of separate future classification and field of search, no reasons exist for dividing among related inventions." *Id.*

Moreover, as required by M.P.E.P. §§ 803 and 816 (quoted above), the Examiner's conclusory statement does not address **the invention as claimed**. The claimed invention is not a molecule. The claimed invention is a method. The reasons for the propriety of the present restriction must be determined from the method claims at issue and not from the properties of the compounds which form one element of the method. Therefore, by not addressing the claimed invention, the conclusion forms a false basis on which to make a restriction requirement. In order to satisfy the requirements of M.P.E.P. § 816, the Examiner must present reasons why the alternative embodiments of the claimed method are properly restricted. No such reasons were provided.

Because the restriction requirement has failed to meet the requirements set-forth in the M.P.E.P., Applicants respectfully request that the requirement be withdrawn.

B. The second restriction requirement is improper because no serious burden would be imposed upon the Examiner if the restriction were not required.

Furthermore, even if reasons to support a basis for the restriction were found and stated, Applicants further traverse the restriction requirement because no serious burden exists to search and examine all the members of the group together. For a restriction requirement to be proper, there **must be a serious burden** upon the examiner if restriction is not required. M.P.E.P. § 803. If the search and examination of an entire application can be made without **serious burden**, the examiner **must** examine it on the merits, even though it includes claims to independent or distinct inventions. *Id.* (emphasis added).

Searching and examining the method of claim 6 in its entirety would present only a nominal additional burden on the Examiner beyond searching any one alternative species of the method. The sequences subject to the present restriction requirement are but one element in a novel method. It is the method as a whole that must be the subject of the Examiner's search. Therefore, any search of the claimed methods must first find every other element of the claimed methods before the number of alternative sequences becomes an issue. As elaborated below, even searching all the sequences recited in claim 6, step (A), would present no burden, because any reasonably constructed automated search for one sequence would reveal whether any of the other sequences are in the prior art.

Furthermore, public policy considerations, which underlie the requirements of M.P.E.P. § 803, strongly favor the examination of the embodiments of the elected claims in a single application. There is an important public interest in the efficient use of Office resources. If SEQ ID NO:1 or any of the polymorphic variants of Table 4 could be found in the prior art, all such instances can be identified in a single automated run of a sequence searching program. Any sequences that differ from SEQ ID NO:1 by a single nucleotide polymorphism, which may identified by the automated search, can then be conveniently compared to the claim concurrently. If each embodiment of the claimed method is searched and examined in a separate application for each variant, the expense in Examiner time and resources will be greatly multiplied. The overhead and expense incurred by the Applicant, the Office, and the public in prosecuting, processing, issuing and maintaining each of the

applications that would be required to provide coverage for the complete invention enormously outweigh any burden to the Office and the Examiner to check a single automated search printout against the few polymorphisms recited in Table 4. The recognition that the public interest is better served by examining related embodiments of an invention in a single application is reflected in 37 C.F.R. § 1.141(a) and M.P.E.P. § 803.

A further public policy consideration against the present restriction requirement relates to the notice function provided by an issued patent. If the embodiments of the present invention are required to be prosecuted in separate applications, the public will be forced to inspect a multitude of separate patents in order to ascertain the true meets and bounds of the claimed invention. With each closely related divisional application issuing at a different time, the important notice function of an issued patent will be severely complicated. Moreover, the public notice function, and agreements between patent rights holders and licensees, may be further impeded if such closely related species of an invention are issued in a multitude of separate patents. Under 35 U.S.C. § 121, divisional applications drawn to the several species of the invention are not subject to any restrictions and may potentially be assigned to a multitude of separate entities.

Therefore, in accordance with M.P.E.P. § 803, 37 C.F.R. § 1.141(a) and in view of the public policy objectives embodied by this section, Applicants respectfully request that the present restriction requirement be withdrawn.

C. The restriction is improper, because it is inconsistent with the provisions of M.P.E.P. § 803.02.

The group of sequences recited in claim 6, step (A), as "the nucleic acid sequence of SEQ ID NO: 1 or a Zmax1 nucleic acid comprising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G)" is a Markush group. M.P.E.P. § 2173.05(h). The M.P.E.P. sets forth particular requirements relating to restrictions for Markush groups at § 803.02.

Under M.P.E.P. § 803.02, first paragraph, the Markush group of Claim 6 should be examined on its merits in its entirety. As set forth there, the Examiner **must** examine all

the members of a Markush group in a claim on the merits, even though they are directed to distinct and independent inventions, when the members are either sufficiently few in number **or** so closely related that a search and examination of the entire claim can be made without **serious** burden.

In the present case, the Markush group of claim 6 recites just 26 single base change polymorphisms of the native Zmax1 sequence. Therefore, any reasonably constructed automated search for sequences related to SEQ ID NO:1 will reveal to the Examiner whether any of the polymorphisms are present in the prior art.

The Examiner states that the polymorphisms of Table 4 are not clearly linked to any SEQ ID NO and that it is unclear how to search the claimed nucleic acid polymorphisms. This is not true. The nature of the Zmax1 sequence and the polymorphisms of Table 4 are clearly described in the specification. The Zmax1 gene comprises SEQ ID NO:1 as disclosed in the specification at page 19, lines 5-6. Thus, the Zmax1 nucleic acids that comprise a polymorphism of Table 4 referred to in claim 6 are polymorphic variants of nucleic acids comprising SEQ ID NO:1. The polymorphisms in Table 4 are identified by their position and base change in one of the contig sequences that comprise the Zmax1 gene. The SEQ ID NOs of the contig sequences are listed in Table 6 at page 125, and the position of the contigs in the Zmax1 gene are illustrated in Figure 5. Therefore, the polymorphisms of Table 4 may be conveniently searched at the same time a search for sequences similar to the Zmax1 sequence (SEQ ID NO:1) is conducted. In view of the small number of polymorphic sites recited in the Markush group of claim 6, Applicants respectfully submit that it would not impose a serious burden to examine the group on the merits in its entirety. Therefore, in accordance with M.P.E.P. § 803.02, first paragraph, the claim must be so examined.

Alternatively, the Restriction Requirement should be modified to conform with M.P.E.P. § 803.02, second through fifth paragraphs. The second paragraph of M.P.E.P. § 803.02 cites the decisions of *In re Weber* and *In re Harnisch* in acknowledging that it is improper for the U.S. Patent and Trademark Office to refuse to examine that which applicants regard as their invention unless the subject matter lacks unity of invention.

In re Weber, 198 U.S.P.Q. 328 (C.C.P.A. 1978); *In re Harnisch*, 206 U.S.P.Q. 300 (C.C.P.A. 1980). The Court of Customs and Patent Appeals (C.C.P.A.), in *Weber*, held that an applicant is entitled to claim his invention with the limitations he regards as necessary to circumscribe that invention within the requirements of 35 U.S.C. § 112. *In re Weber*, 198 U.S.P.Q. at 331. "[A]n applicant has a right to have *each* claim examined on the merits." *Id.* at 331 (emphasis in original). *Harnisch* extends the findings of *Weber* to hold that a determination of propriety of a Markush type claim is based on a unity of invention standard. *In re Harnisch,* 206 U.S.P.Q. at 305. Unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. *See,* M.P.E.P. § 803.02, second paragraph. Alternatively stated, a Markush grouping is proper when the substances have "a community of chemical or physical characteristics" that justify their inclusion in a common group and that such inclusion is not repugnant to principles of scientific classification. *See, e.g.*, *In re Harnisch*, 206 U.S.P.Q. at 305; *In re Jones*, 74 U.S.P.Q. 149, 151 (C.C.P.A. 1947).

In the present case, the Markush group members are structurally related Zmax1 sequences, which contain single base polymorphisms. SEQ ID NO:1 and the Zmax1 sequences having a polymorphism identified in Table 4, except for the C/A base change at location 21119 (308G), could be more generally referred to as "wild-type" Zmax1 sequences. The group members also share at least one common utility as defined by the claim. For example, each such sequence has utility at least in identifying a candidate molecule involved in lipid regulation by comparing the binding or inhibition of binding of a molecule to an HBM sequence and a member of the group of Zmax1 sequences. Further, the claimed nucleic acids comprise members of a common group that is scientifically classifiable, i.e., the grouped members are polymorphisms of the Zmax1 gene that do not appear in every HBM affected individual. One of skill in the art would appreciate that the grouped nucleic acids may be used together in a number of applications. Moreover, the alternative embodiments of the methods using the alternative members of the Markush group have the same utility and may be used together, for example as control methods to

insure that the candidate molecule identified by one embodiment of the method is also identified by other embodiments of the method so that the molecule's effect relates to the HBM sequence and not one of the non-HBM polymorphic variants. Therefore, there is unity of invention in the group of the instant application in accordance with Markush claim practice.

Accordingly, Applicants respectfully request that the restriction requirement, at least, be modified to treat Applicant's election herein as a provisional election as set forth in M.P.E.P. § 803.02, second through fifth paragraphs. If the elected subgroup, is found to be allowable, the elected claims should be examined with respect to additional members of the Markush group.

D. Provisional election with traverse pursuant to 37 C.F.R. § 1.143

Pursuant to 37 C.F.R. § 1.143, Applicants hereby elect, **with traverse** as discussed above, Subgroup i (SEQ ID NO:1).

IV. Conclusion

For at least the forgoing reasons, Applicants request withdrawal of the restriction requirement and Examination of the application in its entirety. Further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any issues relating to this application, it would be appreciated if the Examiner would telephone the undersigned concerning such issues so that prosecution of this application may be expedited.

Respectfully submitted,

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Attachment to the Response Dated August 12, 2002
Marked-Up Claim 6

6. A method for identification of a candidate molecule involved in lipid regulation comprising:

(A) identifying a molecule that binds to, or that inhibits binding of a molecule to, the nucleic acid sequence of SEQ ID NO: 1 or a Zmax1 nucleic acid comprising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G);

(B) identifying a molecule that binds to, or that inhibits binding of a molecule to, the nucleic acid sequence of SEQ ID NO: 2; and

(C) comparing the extent of binding, or the extent of inhibition of binding, of the molecule to each nucleic acid sequence, wherein the molecule that binds, or inhibits binding, more or less to the nucleic acid sequence of SEQ ID NO: 2 or the nucleic acid sequence of SEQ ID NO: 1 or a Zmax1 nucleic acid comprising a polymorphism of Table 4, except for the C/A base change at location 21119 (308G), is the candidate molecule.